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REMARKS

Claims 27-42 are pending in the above-identified application. Applicants have amended the first paragraph of the specification to correct informalities in the priority claim. Accordingly, this application claims the benefit of priority to earliest application serial no. 60/130,089, filed April 20, 1999. Claims 27 and 28 have been amended to recite that the first enzyme is a ligase. Support for these amendments can be found, for example, at pages 22-27 and throughout the application. Claims 37 and 38 have been amended to provide antecedent basis. Support for the amendment can be found in the base claim 27. New claim 43 has been added. Support for this new claim can be found, for example, in claim 27, in Figure 7 and at page 33, paragraphs 1-2. Accordingly, no new matter has been introduced by the amendments and entry thereof is respectfully requested.

Regarding the objections raised with respect to the Information Disclosure Statement and the Drawings. Applicants will forward legible copies of each publication referenced in the Statement filed March 25, 2002, under separate cover. The typographical errors or omitted reference signs to the referenced drawings have been corrected. Specifically, the Brief Description of the Drawings has been amended where appropriate to provide separate descriptions for Figures 6A and 6B, and for Figures 7A-7F. The description of Figure 4 has been amended to recite the reference sign 70. Support for this

amendment can be found, for example, in the paragraph bridging pages 27 and 28, at page 27. Finally, corrected formal drawings for Figures 4, 5A and 5B are submitted herewith which recite the correct reference number 60 instead of 0-60. Support for the corrections can be found in the Brief Description of the Drawings for these figures. Accordingly, the amendments to the specification or correction of the drawings do not introduce new matter and entry of thereof is respectfully requested.

Applicants have carefully considered the rejections in set forth in the Office Action and respectfully traverses all rejections for the reasons that follow.

REJECTIONS UNDER 35 U.S.C. § 112

Claims 27-29 and 31-42 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description for a first enzyme other than a ligase and for a second enzyme other than a polymerase. The Office Action asserts that ligase and polymerase are the only types of first enzyme and second enzymes described, respectively, and that the application lacks any suggestions of other enzymes that can be used in the methods of the invention.

Applicants contend that the application sufficiently describes enzymes other than ligase that can be used as a first enzyme. However, to further prosecution of the above-identified application, Applicants have amended the claims to recite that the hybridization complex is

contacted with a ligase. Therefore, this ground of rejection is moot and Applicants respectfully request that it be withdrawn.

Applicants further contend that the application sufficiently describes enzymes other than polymerase that can be used as a second enzyme. For example, the application describes the use of ligase chain reaction (LCR) and oligo ligase amplification (OLA) at pages 20-22. The application further describes that a 3' exonuclease can additionally be employed in an LCR or OLA reaction (see, for example, page 21, last paragraph). Therefore, the application describes amplification methods that employ, for example, a ligase activity and an exonuclease activity.

The application also describes the use of activities other than polymerase activity in additional amplification methods. For example, pages 27-30, describe invasive cleavage amplifications that can employ, for example, Flap endonucleases such as FEN-1, FEN-2, *AfuFEN1* or *PfuFEN1* (see, for example, page 28, paragraphs 3-4). Further, RNaseH, Exo III and reverse transcriptase are described in conjunction with a cycling probe amplification method at, for example, page 30, paragraph 4. Described on page 15, paragraphs 1 and 2, is the use of endonucleases and polymerases with 5'-3' exonuclease activity in conjunction with strand displacement amplification (SDA). All of the above methods constitute amplification methods that can be used in conjunction with a circularized probe to produce an amplicon. Therefore, the application describes at least

four activities other than polymerase activity that can be used in the claimed methods of the invention. Accordingly, Applicant has sufficiently described activities other than polymerase for the claimed second enzyme and respectfully requests that this ground of rejection be withdrawn.

Claims 27-29 and 31-42 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement for a method which uses a first enzyme other than a ligase and for a method that uses a second enzyme other than a polymerase. In this regard, the Office Action asserts that it would require undue experimentation to search and find enzymes having such other activities including, for example, those enzymes whose activities have not yet been discovered.

Applicants contend that the claims as filed are sufficiently supported by the application to allow those skilled in the art to practice the invention as claimed. First, the claims are commensurate in scope with the teachings of the application because they cover only those first and second enzymes having the activity recited in the claims. Accordingly, the claims are not directed to all possible enzymes. Rather, they are directed to a ligase that causes modification of a circular primer to form a circularized probe and a second enzyme that forms a concatamer. Secondly, claim 27 has been amended above to further prosecution of this application. Accordingly, this ground of rejection is moot with respect to the claimed first enzyme. Finally, the application sufficiently

describes amplification schemes employing enzyme activities other than polymerase that can be used to produced amplicons, including concatamer amplicons. Such other amplification schemes and the amplification activities have been described above with reference to written description and also are applicable with regard to enablement because those skilled in the art would have known how to use the enzymes based on the teaching in the specification and that which was known in the art regarding their activity and conditions of use. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 27-29, 39, 41 and 42 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. In this regard, the Office Action asserts that the recitation of "circular primer" and "circularized probe" is unclear allegedly because the former term implies a molecule without free ends while the latter term implies that the primer has free ends.

Applicants contend that the objected terms are sufficiently clear to allow those skilled in the art to practice the invention as claimed. For example, the application is clear that termini of a hybridized primer is circularized to form a circularized probe when it describes:

[A] single probe is hybridized with a target nucleic acid. Each terminus of the probe hybridizes adjacently on the target nucleic acid and the OLA assay

as described above occurs. When ligated, the probe is circularized while hybridized to the target nucleic acid.

Page 22, paragraph 4. This paragraph goes on to explicitly state that "the probe has no terminus" following circularization. Further, the application again is clear as to the nature of the primers subject to circularization, when it describes:

Ligation of the "primers" (which are the discrete ends of a single oligonucleotide) results in the formation of a modified hybridization complex containing a circular probe probe i.e. an RCA template complex. That is the oligonucleotide is circularized while still hybridized with the target nucleic acid.

Paragraph bridging pages 22 and 23, at page 23.

In light of these descriptions, Applicants maintain that the application is sufficiently clear as to which primers or probes can have free termini and which may not have free termini. Therefore, Applicants respectfully request that this ground of rejection be withdrawn.

Claim 27 stands rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for use of the terms "first enzyme" and "second enzyme" in conjunction with forming a circularized probe or a concatamer amplicon, respectively. In this regard, the Office Action asserts

that it is not clear what other enzymes are encompassed by these terms other than a ligase or a polymerase, respectively.

Applicants contend that the terms are sufficiently clear to allow those skilled in the art to practice the invention as claimed. The term enzyme is well recognized in the art and is described throughout the application. Accordingly, the meaning of this term is not indefinite. Nor is the use in combination with the recited activity. Instead, the rejection appears to reiterate the enablement rejection, which Applicants have addressed previously. Therefore, the term is clear as it is known in the art and the rejection thereof is respectfully requested to be withdrawn.

Claims 27 and 42 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly omitting an essential element. The omitted elements are suggested to be nucleotides required for polymerase activity.

Applicants have described above with reference to the enablement rejection that activities other than polymerase activity can be used to form the claimed amplicons of the invention. Accordingly, the suggested element is unduely restrictive and does not constitute a gap between the claimed elements. Therefore, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 28, 37 and 38 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly lacking antecedent bases for the recitation of "said circular probe" in line 1. Claim 28 recites the term "circular primer" and therefore has proper antecedent basis because it depends from base claim 27. Claims 37 and 38 have been amended above to recite "circular primer" to provide proper antecedent basis with base claim 27. Accordingly, this ground of rejection is moot.

Claim 40 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for use of the term "substantially complementary." The Office Action asserts that this term is a relative term and that the specification fails to provide a standard.

Applicants contend that the term is sufficiently clear to allow those skilled in the art to practice the invention as claimed. The application teaches, for example, on page 12, lines 3-5, that the term "substantially complementary" means that "that the probes are sufficiently complementary to the target sequences to hybridize under normal reaction conditions." Further, such reactions conditions are set forth in detail in the following paragraph on page 12 where the application describes conditions for high, moderate, and low stringency conditions (page 12, first full paragraph). Further, the application exemplifies that such conditions are understood by those skilled in the art by citation of two common laboratory manuals for molecular cloning and molecular biology (page 12, lines 7-8).

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Therefore, the terms are sufficiently definite as claimed because they have art recognized meanings. Moreover, the application provides detailed guidance regarding standards for hybridization conditions of substantially complementary sequences. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. §102

Claims 27-42 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Fan et al., Publication U.S. 2002/0006617 A1. The Office Action alleges that Fan et al. is an invention by another and describes all the elements of the claimed invention. Further, the Office Action alleges that the priority applications for the above-identified application lacks support for the claimed invention. Accordingly, the above-identified application has been accorded a priority date as of the filing date of the parent application, which is March 3, 2000.

While not conceding that Fan et al. constitutes a proper basis for a prior art rejection, Applicants contend that the benefit of priority should be awarded at least to application serial no. 60/135,053, filed May 20, 1999. The claimed invention is supported in this and other applications to which the benefit of priority is claimed. Such other applications include, for example, application serial no. 60/130,089, filed April 20, 1999; application serial no. 60/135,051, filed May 20, 1999; application serial no. 60/135,123, filed May 20, 1999; application

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serial no. 60/161,148, filed October 22, 1999; application serial no. 60/160,917, filed October 22, 1999, and application serial no. 60/160,927, filed October 22, 1999. All of such priority applications have a filing date earlier than the earliest filing date listed on Fan et al., which is February 7, 2000.

The claims are directed to a method of detecting an amplification reaction. The method consists of contacting a circularized probe with an amplification primer and an enzyme to form a concatamer amplicon, cleaving the concatamer and contacting the cleavage products with an array for detection. As set forth below, the priority applications contain each and every element of the claimed invention.

Application serial no. 60/135,053, (the '053 application) teaches the use of arrays for detection of nucleic acids. For example, the application uses the term "array" in its title. Additionally, on page 1, first paragraph, the application teaches that "[m]ultiplex PCR amplification of SNP loci with subsequent hybridization to oligonucleotide arrays has been shown to be an accurate and reliable method of simultaneously genotyping at least hundreds of SNPs." Further, the application teaches:

[T]he DNA template is associated with a solid support. To this end, there are a wide variety of known methods of attaching DNAs to solid supports. Recent work has focused on the attachment of binding ligands,

including nucleic acid probes, to microspheres that are randomly distributed on a surface, including a fiber optic bundle, to form high density arrays. See for example PCT US98/21193 and PCT US98/05025, both of which are expressly incorporated by reference.

Page 3, first full paragraph (emphasis added).

The '053 application further teaches the use of capture probes on subpopulations of microspheres in arrays that hybridize to primers for detection of an amplification product (see, for example, page 4, first full paragraph). The application further describes the use of microsphere arrays throughout pages 1-5 of the section entitled "Invention Disclosure Form." Accordingly, the '053 application teaches steps (e) and (f) of claim 27 directed to contacting an amplicon with an array and detecting the product.

The '053 application further teaches the use of nucleic acid probes and hybridization for detection of a target sequence. For example, the application teaches on page 3, second full paragraph, that the invention is directed to the detection and quantification of differences or variations of sequences using bead arrays. The methods of detection include, for example, ligation chain reaction (LCR or OLA), InvaderTM technology, single base extension technology, competitive probe binding and sequencing by synthesis. Further, the application explicitly states:

Many of these methods require a primer nucleic acid (including nucleic acid analogs) that is hybridized to the target sequence to form a hybridization complex, and an enzyme is added that in some way modifies the primer to form a modified primer; generally, the occurrence of the modification depends on the presence or absence of a particular sequence, thus allowing sequence differentiation.

Page 3, second full paragraph. Exemplary primer configurations are further provided for the LCR, CPT (cycling probe technology) and Invader™. The application summarizes the probe or primer requirement for detection of a target sequence by teaching:

Thus, in general, a target nucleic acid is added [sic] to a reaction mixture that comprises the necessary amplification components, and a modified primer is formed.

Page 4, lines 1-3. Moreover, the entire section entitled "Invention Disclosure Form" provides explicit details for the above methods of detection. Accordingly, the application teaches the elements in steps (a)-(c) of hybridizing a probe or a primer to a target nucleic acid to form a hybridization complex and modifying the probe or primer.

The '053 application further teaches various amplification reactions and the use of amplification probes. Exemplary descriptions can be found, for example,

at page 4, paragraph 3 through page 7, and in the section entitled "Invention Disclosure Form" at, for example, pages 1-5. At page 4, paragraphs 3 and 4, the application teaches that amplification methods can be generally divided into target amplification, which involves increasing the number of target sequences to be detected, and signal amplification, which involves increasing the number of signaling probes to be detected.

Exemplary target amplification methods include the polymerase chain reaction (PCR), strand displacement amplification (SDA) and nucleic acid sequence based amplification (NASBA) (page 3, paragraph 3). Exemplary signal amplification methods include the ligase chain reaction (LCR), cycling probe technology (CPT), InvaderTM technology, Q-Beta replicase (Q β R) technology, and the use of amplification probes such as branched DNA that result in multiple labeled probes. (page 4, lines 1-4). The section entitled "Invention Disclosure Form" further exemplifies amplification of probe and primers using, for example, the oligo ligation assay and allele-specific PCR. Therefore, the application teaches that numerous amplification methods well known in the art can be used for detecting a target molecule by, for example, amplifying the target or by, for example, amplifying the target probe. Accordingly, the '053 application teaches the element in step (c) of the claimed invention directed to amplifying a probe with an amplification primer to form an amplicon.

Further, the '053 application teaches forming a circularized probe as is claimed in step (b) of the application as well as teaches amplifying such a probe with a primer to form a concatamer amplicon as is claimed in step (c). Finally, cleavage products of the concatamer similarly are taught in the '053 application. For example, at page 5, the first full paragraph teaches:

The polymerase chain reaction (PCR) is widely used and described, and involve [sic] the use of primer extension combined with thermal cycling to amplify a target sequence. . . . In addition, there are a number of variations of PCR which also find use in the invention.

(citations omitted). This passage goes on to exemplify ten additional PCR methodologies that can be employed in the amplification of a target or probe sequence. Except for the general method of PCR, none of the additional ten PCR variations are redundant with the other amplification methodologies described above and taught in the '053 application. Therefore, the application exemplifies a large number of different amplification methods well known in the art that can be used for amplicon formation in the methods of the invention.

The application further teaches at page 4, paragraph 3, and at page 5, paragraph 2, that strand displacement amplification (SDA) can be used in the methods of the invention. Further, the application incorporates by reference U.S. Patent Nos. 5,455,166 and 5,130,238 as

exemplary teachings of this method. Applicant draws the Examiner's attention to the fact that amplification of a circular nucleic acid is a strand displacement amplification methodology.

Strand displacement methods also can involve the cleavage of displaced product with, for example, a restriction enzyme as exemplified in the incorporated patents (see, for example, claim 1 of U.S. Patent No. 5,455,166). Moreover, these and other embodiments of strand displacement amplification are further exemplified in the priority application serial no. 60,161,148 at pages 10-11, for example. The '053 application further teaches the use of multiple primers for ligation of probes and primers combined with cleavage enzymes at, for example, the sentence bridging pages 3 and 4. Finally, cyclization of nucleic acids and employment in recombinant or amplification methods were well known in the art. For example, polymerization around a circular single stranded plasmid for site-directed mutagenesis was in use more than 14 years prior to the filing date of the '053 application. Accordingly, the application teaches numerous amplification methods for the detection of amplicons including circular probes and concatamer formation thereof. Strand displacement amplification is a specific example of one such method.

In light of the teachings in the priority '053 application and the remarks above, Applicant contends that the claimed invention is sufficiently supported in this and

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other priority applications to be accorded benefit of their filing dates. Accordingly, Applicant respectfully requests that the rejection over Fan et al. be withdrawn.

REJECTIONS UNDER 35 U.S.C. §103

Claims 27-41 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Taylor, Publication No. US 2002/0168645, and Walt et al., U.S. Patent No. 6,023,540. Claim 42 stands rejected over the additional reference to Lizardi. The Office Action alleges that Taylor describes the detection of nucleic acids using rolling circle amplification where a circular template is hybridized to a sample nucleic acid, followed by addition of a primer, dNTPs and a polymerase to produce an oligonucleotide multimer. The multimer can be cleaved to produce amplified nucleic acid that is detectable using an array of capture probes. The Office Action concedes that Taylor does not teach capture probes attached to microspheres which are randomly distributed on a surface of a substrate, or a substrate being a fiber optic bundle. However, Walt et al. is alleged to describe a microsphere-based system carrying different chemical functionalities positioned in wells randomly distributed in an array. The chemical functionalities are alleged to be capture probes. The Office Action concludes that it would have been obvious to combine the detection methods of Taylor on an array of Walt et al. because the fiber optic sensors of Walt et al. support a large number of chemical functionalities and are easy to produce and use.

To establish a prima facie case of obviousness, the Office must show that the prior art would have suggested the claimed device to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success when viewed in the light of the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000). The first requirement of this test is at issue in the claimed invention because the Office Action simply asserts that fiber optic sensors support a large number of functionalities and are easy to produce and use. However, there has been no showing that such a general conclusion is supported by the cited art.

Establishing that the prior art would have suggested the claimed device requires an underlying factual showing of a suggestion, teaching, or motivation to combine the prior art references and is an "essential evidentiary component of an obviousness holding." *Brown & Williamson Tobacco*, 229 F.3d at 1124-25 (quoting *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1351-52 (Fed.Cir.1998); see also *C.R. Bard* at 1351 (obviousness requires some suggestion, motivation, or teaching in the prior art where to select the components that the inventor selected and use them to make the new device); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000) (there must be some motivation, suggestion or teaching in the prior art of the desirability of making the specific combination that was made by the applicant). The evidentiary showing must be clear and particular and broad conclusory statements about the teachings of the

cited references, standing alone, are not "evidence."
Brown & Williamson Tobacco, 229 F.3d at 1125 (quoting In re Dembiczak, 175 F.3d 994, 1000 (Fed.Cir.1999), abrogated on other grounds by In re Gartside, 203 F.3d 1305, 53 USPQ2d 1769 (Fed.Cir.2000)).

In the pending Office Action, there has been no underlying factual showing that it would have been obvious to one of ordinary skill in the art to have modified the detection methods of Taylor with the array of Walt et al. While not asserting nor conceding that the microsphere-based arrays of Walt et al. support a large number of chemical functionalities or are easy to produce or use, Applicants submit that the required factual showing is missing because the Office Action fails to point to clear and particular language suggesting use of a probe amplification scheme in conjunction with microspheres. Walt et al. appears to describe probe detection methods using detection of a signal from a fluorescent dye (col. 10, lines 8-13, and in Table V). As such, Walt et al. appears to be unconcerned with probe amplification schemes. Therefore, the assertion in the Office Action appears to be nothing more than a conclusory statement, unfounded by supporting evidence. Accordingly, the Office has not established its burden that the showing of a suggestion, motivation or teaching of the claimed combination must be clear and particular.

One purpose of the evidentiary requirement for showing a suggestion, motivation or teaching of the claimed

combination is to prevent impermissible hindsight reconstruction of the claimed invention based on Applicant's own disclosure. C.R. Bard, 157 F.3d at 1352; In re Dembiczak, 175 F.3d 994, 999 ("[c]ombining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight"). In determining the validity of patented biopsy needle assembly over the sole assertion that it arose from obvious adaptations of a single prior art needle assembly to accommodate a new biopsy gun design, the court admonished against hindsight reconstruction when it stated:

The invention that was made, however, does not make itself obvious; that suggestion or teaching must come from the prior art. See, e.g., Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1051-52, 5 USPQ2d 1434, 1438 (Fed.Cir.1988) (it is impermissible to reconstruct the claimed invention from selected pieces of prior art absent some suggestion, teaching, or motivation in the prior art to do so); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed.Cir.1985) (it is insufficient to select from the prior art the separate components of the inventor's combination, using the blueprint supplied by the inventor); Fromson v. Advance Offset Plate, Inc., 755 F.2d 1549, 1556, 225 USPQ 26, 31 (Fed.Cir.1985) (the prior art must suggest to one of ordinary skill in the art the desirability of the claimed combination).

The court went on to conclude that because no prior art provided a teaching, suggestion or motivation for the structure of the claimed needle assembly there was, as a matter of law, an absence of an essential evidentiary component for an obviousness finding. C.R. Bard at 1352.

Similarly, here, the Office Action has taken Applicants' own teachings and used it against them without additional support that the prior art would have suggested, motivated or taught one of ordinary skill to make the claimed combination. As describe above, Walt et al. appears to have been unconcerned with amplification schemes. Similarly, Taylor does not suggest the use of a microsphere step in combination with an amplification scheme. Instead, all of the attachment steps described by Taylor are directed to the positional fixing of a capture to a solid surface by permanent linkages. See, for example, paragraphs 10, 121-122 and 171.

Moreover, Taylor was filed more than two years after the filing date of Walt et al. and is silent as to the combination of an amplification scheme in conjunction with use on microspheres as an additional step or component in an array detection method. The fact that Taylor is silent as to the combination of microspheres with an amplification scheme indicates that Walt et al. could not have provided the suggestion alleged in the Office Action to combine because Taylor would have had knowledge of Walt et al. by the time Taylor filed his application. For example, by the

time Taylor filed the parent utility application on April 16, 1999, Walt et al. had already published his methods in peer reviewed journals. Two such publications include, Karri et al., "Randomly Ordered Addressable High-Density Optical Sensor Arrays," *Analytical Chemistry*, 70:1242-1248 (April 1998), and Walt, D.R., "Bead-Based Fiber-Optic Arrays," *Science*, 287:451-452 (1999), attached hereto as Exhibits A and B, respectively. However, the Taylor application is strikingly silent as to any use of microspheres in conjunction with the array detection methods describe therein.

The Office Action neither cites art showing a combination of microspheres with a probe amplification scheme nor cites to text in the cited references that provide a suggestion, motivation or teaching to combine a rolling circle amplification scheme with microsphere components of an array to achieve the claimed combination. The alleged rationale fails to support any motivation because there is no evidence that the arrays of Taylor did not support a large number of functionalities or were difficult to produce or use.

Reliance on "common knowledge and common sense" to fill the void for the required showing of a suggestion for a claimed combination of elements does not substitute for the obligation to cite references to support an obvious conclusion. In re Lee In re Thrift, 298 F.3d 1357, 1364 (Fed. Cir. 2002). Consequently, such a lack of an evidentiary showing is nothing more than impermissible

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hindsight reconstruction based on reading Applicant's own invention and reliance on unsupported conclusory statements. Applicants therefore respectfully request that the rejection of claims 27-42 be withdrawn.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call David A. Gay or the undersigned attorney.

Respectfully submitted,

8.8.03
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